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BRIEF REPORT

Changes in antimicrobial resistance and outcomes of health care–associated infections

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Abstract

To describe the change in the epidemiology of health care–associated infections (HAI), resistance and predictors of fatality we conducted a nationwide study in 24 hospitals between 2015 and 2018. The 30-day fatality rate was 22% in 2015 and increased to 25% in 2018. In BSI, a significant increasing trend was observed for *Candida* and *Enterococcus*. The highest rate of 30-day fatality was detected among the patients with pneumonia (32%). In pneumonia, *Pseudomonas* infections increased in 2018. Colistin resistance increased and significantly associated with 30-day fatality in *Pseudomonas* infections. Among *S. aureus* methicillin, resistance increased from 31 to 41%.

Key words Health care · associated infections · Blood stream infections · Colistin resistance

Introduction

Health care–associated infections (HAI) represent a huge burden on the health care system worldwide with high morbidity and mortality. Antimicrobial resistance among Gram-negative (GN) bacteria is one of the major public health threats [1, 2]. Collecting data is crucial to estimate the incidence and burden of both HAI and resistance pattern of causative microorganisms [3]. As the study group on HAI, we survey the leading highly resistant bacteria since 2012 in Turkey [1, 4]. By this multicentric study, we described the clinical and microbiological data about the changing epidemiology of HAI in Turkey in 2018 compared to 2015.

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Methods

Study population

This is a retrospective multicentric study in 24 hospitals from different geographic regions of Turkey.

The diagnosis of HAI was based on the Centres for Disease Control and Prevention (CDC) criteria [5]. We described the most common six types of HAI (blood stream infection (BSI), pneumonia, surgical site infection (SSI), gastrointestinal infection (GI), urinary tract infection (UI) and central nervous system infection (CNI). We detailed the most common four GN bacteria and their resistance to carbapenem, quinolone and colistin, and the most common three gram-positive bacteria (Coagulase negative staphylococcus (CNS), *S. aureus*, *Enterococcus*) and their resistance to methicillin, vancomycin and the most common two types of candida. Each case was validated according to the monthly reports of infection control team of each centre.

Microbiological studies

Identification and minimum inhibitory concentration of the microorganisms that are clinically significant were conducted

by automated systems (VITEK 2, Biomerieux, Marcy l'Etoile, France; Phoenix, BD, Franklin Lakes, NJ, USA) in use at each centre according to the Clinical and Laboratory Standards Institute guideline [6].

Statistical analysis

In statistical analysis, Student's *t* test was used for continuous variables and chi-square test was used for the categorical variables. Separate multivariate analyses for leading problem bacteria were performed for the predictors of 30-day fatality. STATA (USA, version 11) was used, and statistical significance was set as < 0.05. Institutional Review Board of Koc University approved the study.

Results

All the consecutive patients with HAI were enrolled; 4182 patients in 2015 were compared with 4105 patients in 2018. Overall, 3894 cases out of 8287 were fatal (47%), and 30-day fatality rate was 23%. While the overall fatality rate was decreasing, the 30-day fatality rate increased from 22 to 25% in 2018. The BSI was the most common (35%) infection and the others were shown at Fig. 1. The BSI and SSI were significantly higher in 2018 than 2015, whereas the pneumonia and UI significantly decreased.

Aetiology of HAI

The most common causative agents of BSI were, *Klebsiella* (20%) and the followed ones were shown at Table 1. We observed that while the proportion of *Candida* and *E. faecalis* infections significantly increased in 2018 compared to 2015 the infections with coagulase negative staphylococcus (CNS) decreased (Table 1). The overall fatality for BSI was 57%, and 30-day fatality was 27%. The 30-day fatality associated with *Acinetobacter* and *Klebsiella* infections increased in 2018 (Table 2). Candida infections were the second most common cause of 30-day fatality in BSI.

In pneumonia, *Acinetobacter* (41%, 36%) was the most common causative pathogen, and the others were shown in Table 1. *A. baumannii* (36–28%) infections (19–15%) decreased while the proportion of *P. aeruginosa infections* significantly increased in 2018 (18%) compared to 2015 (24%) (Table 1). The overall fatality rate was 60% in pneumonia, and 30-day fatality rate was 32%.

The causative agents among SSI, urinary system infections (USI), gastrointestinal infections and central nervous system infections were shown at Table 1. *K. pneumoniae* (20–30%) and *E. coli* infections (26–31%) increased while the proportion of *candida* infections significantly decreased in 2018 (16%) compared to 2015 (2%) (Table 1).

Resistance

The highest rate of carbapenem resistance was seen in *A. baumannii.* There was a significantly increase in carbapenem resistance among *A. baumannii* in 2018 (86–93%) compared to 2015 ($p < 0.001$). The rates of carbapenem resistance for most seen GN bacteria were shown in Table 2.

We observed the highest rate of quinolone resistance in *A. baumannii*. There was a significant increase in quinolone resistance for *K. pneumoniae* (60–72%) and *P. aeruginosa* (33–46) in 2018 compared to 2015 ($p < 0.001$). Colistin resistance was higher for *A. baumannii* (1.4–7%) and *P. aeruginosa* (3–15%) in 2018 than 2015 ($p < 0.001$). We observed a significantly decrease in colistin resistance for *K. pneumoniae* (20–16%) in 2018 compared to 2015.

The proportion of *Enterococcus* increased in 2018; however, the resistance to vancomycin decreased from 13 to 4% ($p < 0.001$). The proportion of methicillin resistant CNS increased from 65 to 72%, ($p = 0.116$). Among the *S. aureus* methicillin resistance significantly increased from 31 to 41% ($p = 0.026$).

In multivariate analysis for *A. baumannii*, pneumonia, age > 65, 2018 compared to 2015 were found to be significantly

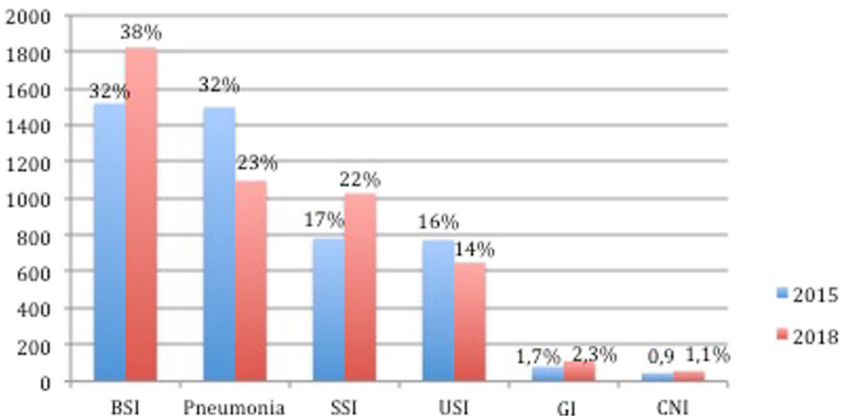

Fig. 1 Comparison of 2018 and 2015 according to the distribution of the sites of health care–associated infections

Table 1 The changing distribution of the microorganisms according to the types of the health care–associated infections

	Bloodstream infections			Pneumonia			Surgical site infections			Urinary system infections			Gastrointestinal infections			Central nervous system infections		
	2015 $n = 1458$ (%)	2018 $n = 1728$ (%)	*p*	2015 $n = 1304$	2018 $n = 837$	*p*	2015 $n = 618$	2018 $n = 783$	*p*	2015 $n = 738$	2018 $n = 631$	*p*	2015 $n = 36$	2018 $n = 79$	*p*	2015 $n = 28$	2018 $n = 47$	*p*
Gram negatives																		
A. baumannii	213 (15)	216 (13)	*0.082**	537 (41)	298 (36)	*0.009**	69 (11)	72 (9)	*0.223*	53 (7)	36 (6)	*0.269*	4 (11)	4 (5)	0.237	4 (14)	4 (9)	*0.433*
K. pneumoniae	292 (20)	333 (20)	*0.592*	283 (22)	167 (20)	*0.332*	94 (15)	104 (13)	*0.303*	150 (20)	187 (30)	*< 0.001**	6 (17)	13(16)	0.977	2 (7)	7 (15)	*0.317*
E. coli	136 (8)	129 (7)	*0.057*	73 (6)	43 (5)	*0.645*	127 (21)	166 (21)	*0.766*	192 (26)	195 (31)	*0.045**	9 (25)	29 (37)	0.215	2 (7)	4 (9)	*0.832*
P. aeruginosa	118 (8)	144 (8)	*0.805*	236 (18)	204 (24)	*< 0.001**	65 (11)	90 (11)	*0.369*	78 (11)	68 (11)	*0.901*	4 (11)	8 (10)	0.872	3 (11)	2 (4)	*0.278*
Gram positives																		
Coagulase negative *Staphylococcus*	169 (12)	131 (8)	*< 0.001**	1 (0,08)	4 (0.5)	*0.060*	49 (8)	78 (10)	*0.188*	2 (0.3)	1 (0.1)	*0.657*	3 (8)	1 (1)	0.055	6 (21)	19 (40)	*0.091*
S. aureus	99 (7)	135 (8)	*0.270*	56 (4)	29 (3)	*0.337*	56 (9)	83 (11)	*0.338*	3 (0.4)	7 (1)	*0.127*	-	1 (1)	NA	4 (14)	2 (4)	*0.121*
E. faeceum	67 (5)	77 (4)	*0.850*	8 (0.6)	3 (0.3)	*0.420*	28 (5)	23 (3)	*0.113*	50(7)	32 (5)	*0.185*	-	2 (3)	NA	2 (7)	1 (2)	*0.283*
E. faecalis	47 (3)	106 (6)	*< 0.001*	4 (0.3)	2 (0.2)	*0.772*	30 (5)	44(6)	*0.525*	26(4)	31 (5)	*0.199*	1 (3)	2 (3)	0.938	3 (11)	3 (6)	*0.503*
Enterococcus spp	11 (1)	19 (1)	*0.350*	4 (0.3)	1 (0.1)	*0.381*	10 (2)	10 (1)	*0.593*	11 (2)	5 (0.7)	*0.230*	-	4 (5)	NA	1 (4)	-	-
Candida	207 (14)	339 (20)	*< 0.001*	-	-	-	-	-	-	117 (16)	13 (2)	*< 0.001**	2 (6)	4 (5)	0.912	1 (4)	4 (9)	*0.406*
C. albicans	86 (6)	125 (6)	*0.131*	-	-	-	-	-	-									
C. parapsilosis	54 (4)	82 (5)	*0.147*	-	-	-	-	-	-									

*$p < 0.05$ was considered statistically significant

Table 2 Antibiotic resistance rates in health care–associated Gram-negative infections

	Carbapenem			Quinolones			Colistin		
	2015	2018	*p*	2015	2018	*p*	2015	2018	*p*
Gram negatives									
Acinetobacter	689/803 (86)	546/587 (93)	*< 0.001**	716/783 (91)	531/564 (94)	*0.064*	12/876 (1.4)	43/620 (7)	*< 0.001**
Klebsiella	393/486 (81)	396/506 (78)	*0.31*	438/730 (60)	517/715 (72)	*< 0.001**	166/825 (20)	129/793 (16)	*0.045**
E. coli	50/123 (41)	62/174 (35)	*0.379*	249/443 (56)	298/506 (59)	*0.404*	5/536 (0.9)	9/558 (1.6)	*0.317*
Pseudomonas	210/289 (73)	264/346 (76)	*0.294*	141/431 (33)	209/452 (46)	*< 0.001**	11/499 (3)	57/508 (15)	*< 0.001**

*$p < 0.05$ was considered statistically significant

associated with the 30-day fatality. In multivariate analysis for *K. pneumoniae,* pneumonia, age > 65, 2018 compared to 2015, BSI, carbapenem resistance were found to be significantly associated with the 30-day fatality. In multivariate analysis for *E. coli*, pneumonia, age > 65, carbapenem resistance were found to be significantly associated with the 30-day fatality. In multivariate analysis for *P. aeruginosa* pneumonia, carbapenem and colistin resistance were found to be significantly associated with the 30-day fatality (Table 3).

Discussion

We present clinical and microbiological data of the HAI from 24 centres of different geographic regions of Turkey. We reported 23% of 30-day fatality rate among our study population. The 30-day fatality rate increased to 25% in 2018 in HAI. The proportion of BSI and SSI were higher in 2018 than in 2015, whereas the proportion of pneumonia and UTI significantly decreased (Fig. 1). Although the improvements in the prevention of device related infections as urinary catheter and mechanical ventilator were observed in the hospitals by years, still improvement is needed in intravenous catheter and postoperative care.

In our previous studies between 2013 and 2015, *Acinetobacter* spp. was the most common cause of gram negative BSI [1, 4]. By this study, *Klebsiella* spp. became as the most common cause of BSI. The 30-day fatality rate associated with *Acinetobacter* and *Klebsiella* infections increased in 2018 compared to 2015. We observed that there is an increase in *Candida* and *Enterococcus faecalis* infections in BSI. Among the most fatal HAIs, *Candida* infections were listed as the second one (33%). In recent studies among all *Candida* species, the 10-day case fatality rate (CFR) was reported as 32% in BSI in Turkey [7], and 30-day mortality of invasive candidiasis in 23 European ICUs was reported as 42% [8].

As recently published articles, the top five pathogens of pneumonia were *Acinetobacter* (32%), *Pseudomonas* (18%), *Klebsiella* (17%), *E. coli* (5%) and *Staphylococcus* (4%) [9]. In our study, pneumonia had the highest CFR (32%) among HAI (Table 1). Increasing rate of *Pseudomonas* infections in pneumonia was remarkable. Inadequate initial treatment of pneumonia due to *Pseudomonas* may be associated with increased mortality rates. We found that carbapenem and colistin resistance and having pneumonia in *Pseudomonas* infections were significantly associated with the 30-day fatality. The 30-day fatality varied from 5 to 33% in the literature [10].

In this study, we analysed the resistance rates of GN bacteria against carbapenem, quinolone and colistin. The

Table 3 Separate multivariate analyses for 30-day fatality in each gram negative bacteria (logistic regression by backward selection). There are four different multivariate analyses for *Acinetobacter*, *Klebsiella*, *E. coli* and *Pseudomonas* species

	Acinetobacter OR (95% CI), p	*Klebsiella* OR (95% CI), *p*	*E. coli* OR (95% CI), *p*	*Pseudomonas* OR (95% CI), *p*
2018 vs 2015	1.79 (1.39–2.30), *P < 0.001**	1.57 (1.15–2.15), *p = 0.004**	2.43 (1.16–5.11), *p = 0.019**	-
Age > 65	1.57 (1.22-2.01), *P* < 0.001	-	2.81 (1.32–5.99), *p = 0.007**	-
Being in ICU	4.21 (2.69-6.57), *p < 0.001**	1.76 (1.10-2.80), *p = 0.017**	14.55 (4.25–49.87), *p < 0.001**	3.61 (1.67–7.76), *p = 0.001**
Pneumonia	-	2.63 (1.91–3.63), *p < 0.001**	-	
BSI	-	-	-	-
R-carbapenem	-	-	-	1.82 (1.08–3.06), *p = 0.023**
R-colistin	-	-		2.85 (1.67–7.76), *p < 0.001**

*$p < 0.05$ was considered statistically significant

resistance rates of quinolone for all pathogens increased in 2018. Resistance to carbapenem was about 90% for *Acinetobacter*, and 80% for *Klebsiella*. These findings were higher than our previous study with BSI [1]. Increasing trend in carbapenem resistance for *Acinetobacter* is an emerging problem for HAI. The resistance to colistin increased for all GN bacteria, except *Klebsiella pneumonia*. Broth microdilution is the only recommended method for colistin antimicrobial susceptibility [11]. Using broth microdilution became more common in recent years and the decrease in colistin resistance among *Klebsiella* can be explained by using inadequate method of antimicrobial susceptibility that had high rate of resistance. It was showed that Vitek-2 System has a variable performance between species of GN bacilli to detect the susceptibility to colistin [12].

There is an increasing trend in quinolone and carbapenem resistance between 2015 and 2018, in Europe. Of the *Klebsiella* isolates in 2018, 78% were resistant to carbapenems, 72% to quinolones and 16% to colistin. The resistance to carbapenem was highest in Greece (63.9%) and quinolone was highest in Poland (68.2%) in a European surveillance study in 2018. We found similar rates of carbapenem and quinolone resistance for *Acinetobacter* with the highest rates in Europe, which were 91.5% and 96.1% in Croatia. In our study, carbapenem resistance among *E. coli* was 38% in 2018, which was very high compared to European countries (2%) [13].

Whereas the proportion of *Enterococcus spp.* increased in 2018, the resistance to vancomycin decreased from 13 to 4% ($p < 0.001$). In a recent multicentric study, vancomycin-resistant enterococcus (VRE) rate was reported as 20.3% [14]. In our study, methicillin resistance was about 70% among CNS. There was a remarkable increase in methicillin resistance for *S. aureus* (MRSA) (31 to 41%) ($p = 0.026$) (Table 2). Mean rate of MRSA was found to be 16.4% in European countries. This was interesting to note that, while MRSA rates are stabilising or decreasing in many of European countries [13], we detected an emerging problem of increasing MRSA in HAI in Turkey. Moreover, MRSA is one of the most common causes of SSI and BSI.

Conclusion

The limited options for antibiotic treatment in carbapenem and colistin-resistant bacteria infections are a serious problem in health care facilities. The BSI and SSI among HAI increased. In BSI, the proportion of *Candida* spp. infections increased. *Pseudomonas* infections were increased in pneumonia. Colistin resistance increased in Pseudomonas spp. and significantly associated with 30-day fatality in *Pseudomonas* infections. Methicillin resistance rate in *S. aureus* significantly increased. The data of 2015 and 2018 allowed us to see the change of the HAI and to address the emerging threats for the future.

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